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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/856,333

08/23/2001

Kathrin Berlin

81669

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23685

7590

04/29/2005

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EXAMINER

SWITZER, JULIET CAROLINE

ART UNIT

PAPER NUMBER

1634

DATE MAILED: 04/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action
Before the Filing of an Appeal Brief**

Application No.

09/856,333

Applicant(s)

BERLIN, KATHRIN

Examiner

Juliet C. Switzer

Art Unit

1634

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11 April 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
(b) ☐ They raise the issue of new matter (see NOTE below);
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

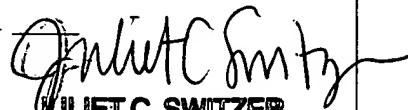
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
The status of the claim(s) is (or will be) as follows:
Claim(s) allowed: _____.
Claim(s) objected to: _____.
Claim(s) rejected: 1-9, 11-16, 18-24, 26, 27 and 30.
Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s).
13. ☐ Other: _____.


JULIET C. SWITZER
PRIMARY EXAMINER
4/25/05

Continuation of 11. does NOT place the application in condition for allowance because:

The remarks have been carefully considered but are not persuasive to overcome the rejection.

Regarding applicant's footnote on page 11, the reference to Herman and Hall is an editorial error, and the statement should read "to have used the methods taught by Griffin to identify mismatches among the sequences being inquired by Hall et al." The examiner regrets the error.

Likewise, noting the inclusion of claims 25, 28 and 29 in the statement of rejection (see response page 12), the examiner agrees that these claims have been cancelled and therefore their presence in the statement of rejection in the final office action should be disregarded.

The claims have been amended to recite methods "consisting of" the recited steps. The methods taught by the combination of Rice et al. in view of Gifford are applied to even these amended claims because the suggested method of the rejections of record would include all of these steps and would not require any steps outside of those recited. Each of the steps recited, for example in claim 1, include a number of different manipulations for the practice of the claimed step, and each is reasonably broad in nature. For example, Applicants argue on page 12 that the amendment of the claims to replace the transition term "comprising" with "consisting of" results in the claims now specifically excluding a sequencing step after fragments containing heteroduplexes are identified. However, this is not entirely accurate. First, claim 1 does not specifically include an "identifying" step as referred to in the argument. Instead, the final step of claim 1 recites "determining the position of 5-methylcytosine in the sample genomic DNA based on the presence and position of the detectable label." This step, as recited, could reasonably include a step wherein the "determining the position" occurs by sequencing the labeled molecules and noting the nucleotide present at the labeled position- thus determining the position "based on the presence and position of the detectable label." Thus, even the claims which are narrowly drawn using "consisting of" language have sufficient breadth so as to include a potential sequencing step. The method suggested by Rice in view of Gifford (and the additional cited references for later claims) would have made obvious even the narrowly drawn claim as currently pending.

At page 13 of the response, applicant points out that Rice et al. does not teach or suggest any of steps (d)-(f) of claims 1 or 30, and that the rationale used by the office to set forth the obviousness rejection is flawed because "it presupposes that one of ordinary skill in the art at the time of the invention would have been interested in knowing sites of cytosine methylation in a sample segment, without also knowing the entire sequence of the segment." This is not persuasive because (1) Rice et al. are in fact most interested in percent methylation at 30 CpG sites as compared to sites "within the known BRCA1 sequence" (p. 1181), they are not discovering or setting forth a newly discovered sequence and (2) even if Rice et al. were most interested in the sequence and the sequence context, Gifford specifically suggests that their method include a step to "determine the identity and position of the mismatch by determining the nucleotide sequence of the mismatch region (Col. 4, lines 7-9)." As previously noted in this action, the currently drawn claims do not exclude such determination, but only require that the determining of the position is "based on the presence and position of the detectable label." This step taught by Gifford is reasonably a method for carrying out such determination based on the presence and position of the detectable label.

Applicant points out that bisulfite treatment modifies sites of unmethylated cytosines, as is also stated in Rice et al. and in the rejection (page 14 of response, first full paragraph). Applicant further states that such treatment results in dramatic change to the treated sequence, and that insofar as the examiner envisions bisulfite treatment as a mechanism for introducing a mutation the Office is in error "on multiple accounts." However, these multiple accounts are not mentioned, instead, the remarks continue with a second point. It is noted that Gifford specifically teaches that mismatched base pairs can arise via a variety of mechanisms, including "chemical modification of DNA (Col. 2, lines 50-51)." Thus, base differences between two sequences introduced via chemical modification (such as bisulfite treatment) clearly fall within the differences discussed by Gifford et al. Applicant further argues that after treatment with bisulfite, two strands which were formally complementary normally do not anneal due to differences in sequence, and accordingly mismatching cannot occur. This is not persuasive. First, it is an attorney argument which is not supported by evidence on the record. Second, Rice et al. teach subsequent amplification of the treated molecules to produce a double strand which could then be compared to a reference sequence which was also bisulfite treated (Rice teaches comparing the bisulfite treated molecules to the "known" BRCA1 sequence), and the claimed method also encompasses the comparison of any of the bisulfite treated molecules of Rice et al. to one another in order to determine differences in methylation among them. The bisulfite treated molecules would only have differences at points of differential methylation, and thus would anneal. The rejection is maintained in view of these remarks.

Applicant attempts to construe Gifford as only being applicable to random event mutations, but this reading of Gifford is narrower than Gifford suggests, as previously noted where Gifford discusses different methods that mismatches are the result of chemical treatment of sequences. Finally, applicant's remarks regarding the "ascertainment of the sequence context" have been previously addressed in this advisory action. Therefore, having carefully considered applicant's remarks, the rejection is MAINTAINED.